Chris Holsinger
Professor, Head and Neck Surgery
Stanford University

Results of Surgical De-intensification & Controversies in the management of HPV+ Oropharynx Cancer

Oropharyngeal carcinoma (OPC) represents a significant public health problem worldwide, affecting nearly 51,000 individuals this year alone in the United States. In the past, surgical options for patients with for OPC was performed through transfacial, transmandibular incisions, yet many patients still required extensive adjuvant therapy postoperatively. Poor function and concern for cosmesis led multidisciplinary teams to explore alternative options, such as concurrent chemotherapy with radiation therapy (chemoRT). Since 1999, with the publication of GORTEC 94-01, chemoRT became the standard of care for organ-preservation approaches for OPC.

Although effective in terms of locoregional control, chemoRT can be associated with significant delayed toxicity, as well as adverse functional effects. Dysphagia remains perhaps the most important functional impairment in survivors of OPC. Late grade 3 to 4 laryngopharyngeal toxicity more than 5 years after treatment was reported in 35% of 101 survivors of OPC who had adequate baseline function in a pooled analysis of three Radiation Therapy Oncology Group (RTOG) trials of concomitant chemoradiotherapy, and the 3-year prevalence of dysphagia approaches 50% based on population-level data from survivors of OPC in the Surveillance, Epidemiology, and End Results–Medicare database. With the recent publication of the first prospective data demonstrating the value of intensity-modulated proton-radiation therapy (IMPT) for head and neck cancer, it is hoped that late effects beyond the acute and subacute treatment window will also be reduced, although data here are lacking. Therefore, despite the advantages of nonsurgical organ preservation offered by chemoRT, concerns about long-term toxicity and swallowing.

Chris Holsinger
Professor, Head and Neck Surgery
Stanford University

Dating as far back as 2011, Chaturvedi et al described the striking association between oropharyngeal cancer (OPC), human papillomavirus (HPV), and the startling new epidemiology of this disease. From 1988 to 2004, HPV-positive OPC increased by 225% (95% CI, 208% to 242%; from 0.8 per 100,000 to 2.6 per 100,000), whereas the incidence of HPV-negative cancers declined by 50% (95% CI, 47% to 53%; from 2.0 per 100,000 to 1.0 per 100,000). Patients with HPV-associated OPC tend to be nonsmokers, male, and younger than traditional patients with head and neck cancer. Does this evolving epidemiology of OPC change the role of surgery within the multidisciplinary treatment paradigm?

Surgery and post-operative radiation therapy (PORT) is a standard treatment paradigm aimed at ensuring locoregional control and survival in patients with head and neck cancer (HNC). The philosophy behind this approach emerged in the 1960's and 1970's, prior to the advent of advanced imaging and understanding of molecular basis of HPV-associated oropharyngeal cancer. Over time, specific adverse features such as perineural invasion, margin distance, and the number and character of metastatic regional lymph nodes (LNs) were identified as "intermediate-risk" factors, and positive margins and extranodal extension of LNs were identified as "high-risk" pathologic predictors of locoregional relapse. The addition of chemotherapy to PORT provided better results in patients with "high-risk" features, but incurred increased toxicity in two prospective clinical trials, RTOG 9501 and EORTC 22931.

However, with regard to HPV+OPC, these traditional predictors of locoregional disease control (LRC) and survival have likewise been applied to patients undergoing transoral minimally invasive endoscopic H&N Surgery (with surgical robotics or the CO2 laser). However, because of the improved clinical outcomes seen in HPV+ OPC, there has been ongoing interest in testing reductions of therapy.

The randomized phase 2 clinical trial Eastern Cooperative Oncology Group 3311 (ECOG3311) demonstrated that patients who had "intermediate-risk" surgical pathology endpoints could receive a decreased radiation dose of PORT of 50 Gy – without apparent declines in LRC or survival compared to patients receiving 60 Gy. This trial indicates that "intermediate-risk" patients treated with frontline surgical therapy may be candidates for careful deintensification. However, this approach remains controversial, in part because of the broad range of characteristics included as eligible for randomization in this study and the relative lack of personalized selection.

Chris Holsinger
斯坦福大学耳鼻咽喉头颈外科
临床教授

HPV相关口咽癌外科降阶治疗的结果和争议

口咽癌（OPC）是一个重要的全球范围的公共卫生问题，仅今年美国就近51,000人罹患该疾病。以前对于口咽癌患者的手术选择是通过面部及颏下切口进行的，但仍有许多患者需要术后较大范围的辅助治疗。术后功能影响和对外形的关注促使多学科团队探索替代选择方案，例如放化疗联合治疗（chemoRT）。自1999年以来，随着GORTEC 94-01的发表，chemoRT已成为口咽癌器官保留治疗的标准。

尽管在局部区域控制方面有效，但chemoRT可能与显著的迟发毒性及不良功能影响相关。吞咽困难可能是口咽癌患者中最首要的功能障碍。在三项放射治疗肿瘤学研究组（RTOG）对放疗化疗联合治疗的101名口咽癌患者的合并分析中，35%的患者在治疗5年喉报告了3至4级晚期喉咽迟发毒性，基于对Surveillance、Epidemiology和End Results-Medicare数据库中的口咽癌患者进行的人口数据分析，治疗后3年吞咽困难的患病率接近50%。随着首个前瞻性研究数据发表，提示了调强质子放射治疗（IMPT）在头颈癌中的价值。研究者希望在急性和亚急性治疗窗口之外的迟发效应也会减少，尽管这方面的研究数据还比较缺乏。总之，尽管chemoRT提供了非手术器官保留的优势，但人们对长期毒性和吞咽功能影响的担忧仍然存在。

早在2011年，Chaturvedi等人就描述了口咽癌（OPC）、人乳头瘤病毒（HPV）之间的显著关联及新流行病学研究。从1988年至2004年，HPV阳性的口咽癌患者增加了225%（95% CI，208%至242%；从每10万人中的0.8增加到每10万人中的2.6），而HPV阴性癌症的发病率下降了50%（95% CI，47%至53%；从每10万人中的2.0下降到每10万人中的1.0）。与传统的头颈癌患者相比，HPV相关的OPC患者往往是不吸烟者、男性，并且年龄较小。这种口咽癌流行病学的变化是否改变了手术在多学科治疗中的作用？

Chris Holsinger
斯坦福大学耳鼻咽喉头颈外科
临床教授

手术和术后放疗（PORT）是治疗头颈癌（HNC）患者的标准治疗方案，旨在确保局部区域控制和提高生存率。这种理念可以追溯到20世纪60、70年代，甚至在影像学不断发展和对HPV相关口咽癌分子研究出现之前。随着时间的推移，特定的预后不良特征点，如神经侵犯、切缘距离以及转移区域淋巴结（LNs）的数量和性质，被确定为“中风险”因素，而切缘阳性和LN的包膜外侵犯被确定为局部区域复发的“高风险”病理预测因子。在PORT中加入化疗在具有“高风险”特征的患者中提供了更好的结果，但在两项前瞻性临床试验RTOG 9501和EORTC 22931中也提高了毒性。

然而，对于HPV阳性的口咽癌患者，这些传统的局部区域疾病控制（LRC）和生存的预测因子同样适用于接受经口微创内窥镜头颈手术（使用手术机器人或CO2激光）的患者。随着HPV阳性的口咽癌患者患者的临床预后改善，一直存在放疗计量减弱的相关研究。

随机Eastern Cooperative Oncology Group 3311（ECOG3311）2期临床试验表明，具有“中风险”手术病理终点的患者可以接受降低PORT放疗剂量（50 Gy），而与接受60 Gy的患者相比，局部区域控制或生存率似乎没有下降。这项试验表明，接受一线手术治疗的“中风险”患者可能是放疗计量减弱治疗方案的候选人。这种方法仍然存在争议，部分原因是这项研究中作为随机化的可选特征范围较广，且缺乏个体化选择。